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THE COMBINATION OF PSYCHOTHERAPY AND PHARMACOTHERAPY IN THE TREATMENT OF ADULT DEPRESSION: A COMPREHENSIVE META-ANALYSIS

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Abstract

No meta-analysis in the field of depression has examined the effects of combined treatment compared with pill placebo, nor has any meta-analysis integrated the comparison of combined treatment against pharmacotherapy alone and psychotherapy alone (i.e., mono treatments). In this comprehensive meta-analysis, we found that combined treatment had a moderate effect on depression compared with pill placebo (g=0.46), and small to moderate effects compared against pharmacotherapy (g=0.38) alone, psychotherapy (g=0.34) alone, and psychotherapy plus placebo (g=0.23). There were some indications for publication bias when combined therapy was compared against placebo (adjusted effect size g=0.31). In multivariate metaregression analyses we found no significant differential predictors for the four comparisons. There were some indications that the use of interpersonal psychotherapy in the combined treatment was associated with a smaller effect size, but this has to be considered with caution, because of the correlational nature of this association. Despite limitations (small number of studies; suboptimal quality of studies) this meta-analysis suggests that combined treatment of depression may be the best treatment available for adult depression, and that it is significantly more effective than placebo, pharmacotherapy alone, psychotherapy alone and the combination of psychotherapy and placebo.

Keywords: depression; major depressive disorder; pharmacotherapy; psychotherapy; combination therapy; cognitive behavior therapy; interpersonal psychotherapy; SSRI; TCA; meta-analysis.

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Introduction

It is well-established that psychological and pharmacological therapies are effective in the treatment of adult depression. Several types of psychotherapy have been shown to be effective, including cognitive behavior therapy (Gloaguen, Cottraux, Cucherat, & Blackburn, 1998; Cuijpers, Berking, Andersson, Quigley, Kleiboer, & Dobson, 2013), interpersonal psychotherapy (Cuijpers, Geraedts, van Oppen, Andersson, Markowitz, & van Straten, 2011), behavioral activation therapy (Ekers, Richards, & Gilbody, 2008), problem-solving therapy (Malouff, Thorsteinsson, & Schutte, 2007), counseling (Cuijpers, Driessen, Hollon, van Oppen, Barth, & Andersson, 2012), and possibly psychodynamic therapy (Shedler, 2010). Dozens of trials directly comparing different types of psychotherapy have also shown that there are no or only small differences between the effects of these therapies and that all therapies seem to be about equally effective. In addition, guided self-help treatments including internet-based treatment (Cuijpers, Donker, van Straten, & Andersson, 2010; Andersson, & Cuijpers, 2009) and group treatments (Cuijpers, van Straten, & Warmerdam, 2008) appear to be as effective as face-to-face treatments with one therapist and one patient. Several types of antidepressant medications have also been found to be effective, including tricyclic antidepressants, SSRIs and several others (Bauer, Pfennig, Severus, Whybrow, Angst, Möller, et al., 2013). Several hundreds of trials directly comparing different types of medication have also shown that all these medications are most likely about equally effective (Gartlehner, Hansen, Morgan, Thaler, Lux, Van Noord, et al., 2012). In addition, dozens of direct comparisons between psychotherapies and pharmacotherapies have shown that psychotherapies and pharmacotherapies are also equally effective or approximately equally effective (Cuijpers, Sijbrandij, Koole, Andersson, Beekman, & Reynolds, 2013). This suggests that all psychological and pharmacological treatments of adult depression are equally effective or about equally effective for mild to moderate depression, although this may not pertains to more chronic forms of depression and dysthymia (Cuijpers, van Straten, Schuurmans, van Oppen, Hollon, & Andersson, 2010).

The combination of psychotherapy and pharmacotherapy, however, has been shown to be more effective then pharmacotherapy alone (de Maat, Dekker, Schoevers, & de Jonghe, 2007; Cuijpers et al., 2014), psychotherapy alone (Pampallona, Bollini, Tibaldi, Kupelnick, & Munizza, 2004), and the combination of psychotherapy and placebo (Cuijpers, Turner, Mohr, Hofmann, Andersson, Berking, et al., 2011). Combined treatment seems to be, therefore, the most effective treatment currently available for adult depression.

The mechanisms behind the added effect of combining treatments is largely unknown. One possible mechanism would be that different patients respond to different treatments and hence providing two treatments would result in more patients improving. However, it is also possible that the two treatment

formats (for simplicity we here assume that pharmacotherapy and psychotherapy are two separate forms of treatments bearing in mind that there are different forms of both pharmacotherapy and psychotherapy) interact. An example of this could be if a patient gets initial help from the psychotherapy, then additional boost from medication, and then additional help from the skills and insights gained in psychotherapy. However, placebo effects appear to ubiquous in depression treatments in particular when there is contact with the study coordinators (Posternak & Zimmerman, 2007), and hence there is a need to elucidate how well combined treatment works against placebo only and indeed also single treatments.

No meta-analysis has examined the effects of combined treatment against pill placebo only. As mentioned earlier, there have been meta-analyses in which combined treatment was compared with pharmacotherapy alone and with psychotherapy alone (De Maat et al., 2007; Cuijpers et al., 2014; Pampanolla et al., 2004), but no meta-analysis has examined all studies in which combined treatment was compared with any other treatment or placebo. We think this is important to examine further, not only because combined treatment may be the most effective treatment currently available, but also because the comparative effects of combined treatment versus pharmacotherapy and those of combined treatment versus psychotherapy have not yet been compared with each other. Combined treatment has been shown to be more effective than pharmacotherapy and psychotherapy alone, but whether these differences are comparable has never been examined in meta-analytic research.

We decided therefore to conduct a comprehensive meta-analysis in which combined treatment was compared with placebo-only, with psychotherapy, with pharmacotherapy and with the combination of psychotherapy and placebo.

Methods

Identification and selection of studies

We used a database of papers on the psychological treatment of depression that has been described in detail elsewhere (Cuijpers, van Straten, Warmerdam, & Andersson, 2008), and that has been used in a series of earlier published meta-analyses (www.evidencebasedpsychotherapies.org). This database has been continuously updated through comprehensive literature searches (from 1966 to January 2014). In these searches, we examined 14,164 abstracts from Pubmed (3,638 abstracts), PsycInfo (2,824), Embase (4,682) and the Cochrane Central Register of Controlled Trials (3,020). These abstracts were identified by combining terms indicative of psychological treatment and depression (both MeSH terms and text words). For this database, we also checked the primary studies from earlier meta-analyses of psychological treatment for depression to ensure that no published studies were missed. From the 14,164 abstracts (10,474 after removal of duplicates), we retrieved 1,476 full-text papers for possible inclusion in the database.

We included (1) randomized controlled trials (2) in adults with a depressive disorder, in which (3) a combined treatment (consisting of a psychological and a pharmacological intervention) (4) was compared to (a) a pill placebo only control condition, (b) pharmacotherapy only, (c) psychotherapy only, (d) or a psychotherapy plus pill placebo condition.

Depression could be defined as major depressive disorder or unipolar mood disorder (including dysthymia), according to a diagnostic interview (such as the DISC, CIDI, or SCAN), or as clinically relevant depressive symptoms according to a score above a cut-off on a depression rating scale. We excluded studies in inpatients, in children and adolescents ($\leq$ 18 years). Comorbid general medical or psychiatric disorders were not used as an exclusion criterion. No language restrictions were applied, except for Chinese.

Quality assessment and data extraction

We assessed the validity of included studies using four of the six criteria of the 'Risk of bias' assessment tool, developed by the Cochrane Collaboration (Higgins & Green, 2008). This tool assesses possible sources of bias in randomized trials, including the adequate generation of allocation sequence; the concealment of allocation to conditions; the prevention of knowledge of the allocated intervention (masking of assessors); and dealing with incomplete outcome data (this was assessed as positive when intention-to-treat analyses were conducted, meaning that all randomized patients were included in the analyses).

We also coded additional aspects of the included studies, including participant characteristics (recruitment method: community, from clinical samples, or other; target group: adults in general, or more specific target groups such as older adults), psychotherapy characteristics (format: individual, group, or guided self-help; number of sessions; and type of psychotherapy: cognitive behavior therapy, interpersonal psychotherapy, or other type); type pharmacotherapy (SSRI, TCA, other), and study characteristics (type of comparison: placebo, pharmacotherapy, psychotherapy, psychotherapy plus placebo; and country: US, UK, Europe, other).

Meta-analyses

For each comparison between a combined treatment and one of the comparison groups, the effect size indicating the difference between the two groups at post-test was calculated (Hedges's g). Effect sizes were calculated by subtracting (at post-test) the average score of the combined treatment group from the average score of the control group, and dividing the result by the pooled standard deviation. Because several studies had relatively small sample sizes, we corrected the effect size for small sample bias according to the procedures suggested by Hedges and Olkin (1985).

In the calculations of effect sizes, we used only those instruments that explicitly measured symptoms of depression, such as the HAM-D (Hamilton,

1960), or the Beck Depression Inventory (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). If more than one depression measure was used, the mean of the effect sizes was calculated, so that each comparison yielded only one effect. If dichotomous outcomes were reported without means and standard deviations, we used the procedures of the Comprehensive Meta-Analysis software (version 2.2.021) (see below) to calculate the standardized mean difference.

To calculate pooled mean effect sizes, we used the computer program Comprehensive Meta-Analysis. Because we expected considerable heterogeneity among the studies, we employed a random effects pooling model in all analyses.

Because the standardized mean difference (Hedges' g) is not easy to interpret from a clinical perspective, we transformed these values into the number-needed-to-treated (NNT), using the formulae provided by Kraemer and Kupfer (2006). The NNT indicates the number of patients that have to be treated in order to generate one additional positive outcome (Laupacis, Sackett, & Roberts, 1988).

As a test of homogeneity of effect sizes, we calculated the I^2-statistic as an indicator of heterogeneity in percentages. A value of 0% indicates no observed heterogeneity, and larger values indicate increasing heterogeneity, with 25% as low, 50% as moderate, and 75% as high heterogeneity. We calculated 95% confidence intervals around I^2 (Ioannidis, Patsopoulos, & Evangelou, 2007), using the non-central chi-squared-based approach within the heterogi module for Stata (Orsini, Higgins, Bottai, & Buchan, 2005). We also calculated the Q-statistic, but only report whether this was significant.

Subgroup analyses were conducted according to the mixed effects model (Borenstein, Hedges, Higgins, & Rothstein, 2009), in which studies within subgroups are pooled with the random effects model, while tests for significant differences between subgroups are conducted with the fixed effects model. For continuous variables, we used meta-regression analyses to test whether there was a significant relationship between the continuous variable and effect size, as indicated by a Z-value and an associated p-value.

Multivariate meta-regression analyses in which more than one predictor was entered simultaneously were conducted in STATA/MP 11.0 for Mac, because these analyses cannot be conducted in Comprehensive Meta-analysis. In order to avoid collinearity, we first calculated the correlation between predictors but found no correlation higher than $r = 0.50$.

Publication bias was tested by inspecting the funnel plot on primary outcome measures and by Duval and Tweedie's trim and fill procedure (2000), which yields an estimate of the effect size after the publication bias has been taken into account (Borenstein et al., 2009). We also conducted Egger's test of the intercept to quantify the bias captured by the funnel plot and test whether it was significant.

Results

Selection and inclusion of studies

After examining a total of 14,902 abstracts (10,992 after removal of duplicates), we retrieved 1,613 full-text papers for further consideration. We excluded 1,560 of the retrieved papers. The flowchart describing the inclusion process, including the reasons for exclusion, is presented in Figure 1. A total of 53 studies met inclusion criteria.

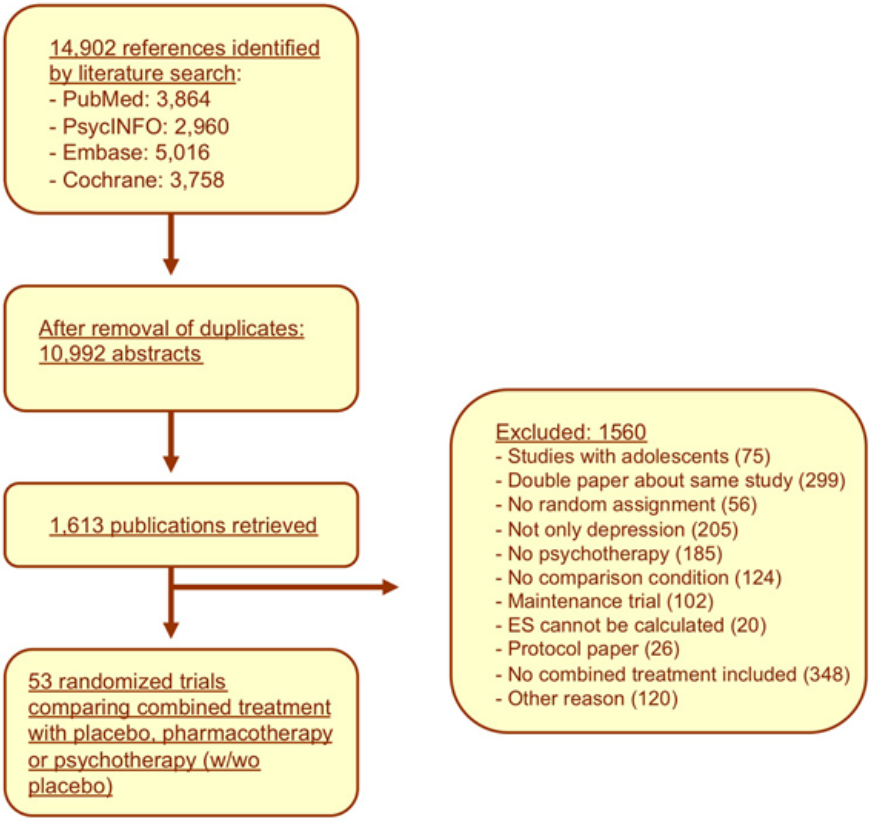

Figure 1. Flowchart of inclusion of studies

Characteristics of included studies

The 53 studies included 4,740 participants, 182 in the placebo-only groups (6 comparisons), 1585 in the pharmacotherapy groups (41 comparisons), 731 in the psychotherapy groups (19 comparisons), and 427 in the psychotherapy plus placebo groups (17 comparisons).

Table 1. Selected characteristics of studies comparing combined treatment with placebo, pharmacotherapy, psychotherapy and psychotherapy plus placebo (N=53).

	Compa-risons [a)]	Recruit-ment	Target group	Depression	Psy Type	Format	N_{ses}	Medica-tion	Quality [b)]	C
Appleby, 1997	PH PL PP	Other	PPD	Mood	CBT	Ind	6	SSRI	+ – + +	UK
Beck, 1985	PS	Comm	Adults	Mood	CBT	Ind	20	TCA	– – – –	US
Bellack, 1981	PH PP	Comm	Adults	Mood	Other	Ind	12	TCA	– – + –	US
Bellino, 2006	PH	Clin	Borderline	MDD	IPT	Ind	16	SSRI	– – + –	EU
Blackburn, 1981	PH PS	Clin	Adults	MDD	CBT	Grp	15	TCA	– – – –	US
Bloch, 2012	PP	Other	PPD	MDD	Dynamic	ind	12	SSRI	+ + + +	ISR
Blom, 2007	PH PS PP	Clin	Adults	MDD	IPT	Ind	12	Snri	– – + +	EU
Browne, 2002	PH PS	Comm	Adults	Mood	IPT	Ind	10	SSRI	+ + + –	CA
Burnand, 2002	PH	Clin	Adults	MDD	Dynamic	Ind	10	TCA	– – + –	EU
De Jonghe, 2001	PH	Clin	Adults	MDD	Dynamic	Ind	16	Other	– – + +	EU
De Jonghe, 2004	PS	Clin	Adults	MDD	Dynamic	Ind	16	Other	– – + –	EU
De Mello, 2001	PH	Clin	Adults	Mood	IPT	Ind	16	Rima	– – + –	BR
Denton, 2012	PH	Comm	Adults	MDD	Other	Ind	15	Other	+ + + +	US
Dozois, 2009	PH	Clin	Adults	MDD	CBT	Ind	15	Other	– + – –	CA
Finkelzeller, 2009	PH PS	Other	Medical	MDD	IPT	Grp	12	SSRI	+ – + +	EU
Friedman, 1975	PH PL PP	Clin	Adults	Other	Other	Ind	12	TCA	– – + –	US
Hautzinger, 1996	PH PS	Clin	Adults	Mood	CBT	Ind	24	TCA	– – + +	EU
Hellerstein, 2001	PH	Clin	Adults	Mood	Other	Grp	16	SSRI	– – – +	US
Hernandez, 2004	PP	Comm	Alcohol	MDD	SUP	Ind	8	SNRI	– – + +	US
Hollon, 1992	PH PS	Clin	Adults	MDD	CBT	Ind	20	TCA	– – + +	US
Hsiao, 2011	PH	Clin	Adults	MDD	Other	Ind	8	Other	+ – + +	TW
Keller, 2000	PH PS	Clin	Adults	Mood	Other	Ind	18	SNRI	+ + + +	US
Lam, 2013	PH	Comm	Adults	MDD	CBT	Ind	8	SSRI	+ + + +	CA
Lesperance, 2007	PH PL PP	Comm	Medical	MDD	IPT	Ind	12	SSRI	+ + + +	CA
Lynch, 2007	PH	Clin	Person dis	Other	Other	Grp	28	Other	– – – –	US
Macaskil, 1996	PH	Clin	Adults	MDD	CBT	Ind	30	TCA	– – – –	UK
Maina, 2010	PH	Clin	Ocd	MDD	Dynamic	Ind	13	SSRI	+ + + +	EU
Maldonado 1984a	PH	Clin	Adults	Mood	CBT/SST	Ind	10	Other	– – + –	EU
Markowitz, 1998	PS	Comm	Medical	Other	SUP	Ind	16	TCA	+ + + +	US
Markowitz, 2005	PH PS	Comm	Adults	Mood	IPT	Ind	17	SSRI	+ + + +	US
McGrath, 1996	PP	Comm	Alcohol	Mood	Other	Ind	12	TCA	– – – +	US
Misri, 2004	PH	Clin	PPD	Mood	CBT	Ind	12	SSRI	+ – + +	CA
Mitchell, 2009	PH	Other	Medical	Other	Other	Ind	9	Other	+ + + +	US
Moak, 2003	PP	Comm	Alcohol	Other	CBT	Ind	12	SSRI	– – – +	US
Murphy, 1984	PH PS PP	Clin	Adults	MDD	CBT	Ind	20	TCA	+ + – +	US
Mynors, 2000	PS PH	Clin	Adults	MDD	PST	Ind	6	SSRI	+ + + +	UK
Naeem, 2011	PH	Clin	Adults	MDD	CBT	Ind	9	SSRI	+ + + +	PA
Ravindran, 1999	PH PL PP	Comm	Adults	Mood	CBT	Grp	12	SSRI	+ + + –	CA
Reynolds, 1999	PH PL PP	Comm	Elderly	MDD	IPT	Ind	16	TCA	– – + +	US
Roth, 1982	PS	Comm	Adults	MDD	Other	Grp	12	TCA	– – – –	US
Rush, 1981	PS	nr	Adults	MDD	CBT	Ind	20	TCA	– – + +	US
Schiffer, 1990	PP	Other	Medical	MDD	Other	Ind	5	TCA	– – – –	US
Shamsaei, 2008	PH PS	Clin	Adults	MDD	CBT	Ind	8	SSRI	+ – + –	IR
Sirey, 2005	PH	Clin	Elderly	MDD	Other	Ind	5	Other	– – + +	US
Stravynsky, 1994	PS	Clin	Adults	MDD	CBT	Grp	12	TCA	– – + –	CA
Targ, 1994	PP	Comm	Medical	Mood	Other	Grp	12	SSRI	– – + –	US
Thompson, 2001	PH PS	Comm	Elderly	MDD	CBT	Ind	18	TCA	– – – +	US
Weissman, 1979	PH PS	Clin	Adults	MDD	IPT	Ind	16	TCA	– – + –	US
Wiles, 2008	PH	Other	Adults	Mood	CBT	Ind	16	Other	+ + + +	UK
Wiles, 2013	PH	Clin	Adults	MDD	CBT	Ind	12	Other	+ + + +	UK
Wilson, 1982	PH PL PP	Comm	Adults	Other	BA	Ind	7	TCA	– – + –	AU
Yang, 2009	PP	Clin	Adults	MDD	Other	Grp	8	SSRI	+ – + +	TW
Zisook, 1998	PP	Clin	Medical	MDD	SUP	Grp	8	SSRI	– – + +	US

[a)] This column indicates the comparisons that are examined in the studies. PH: combined versus pharmacotherapy; PS: combined versus psychotherapy; PP: combined versus psychotherapy plus placebo; PL: combined versus placebo.

Table 1 (continued). Selected characteristics of studies comparing combined treatment with placebo, pharmacotherapy, psychotherapy and psychotherapy plus placebo (N=53).

[b)] In this column a positive or negative sign is given for four quality criteria, respectively: allocation sequence; concealment of allocation to conditions; blinding of assessors; and intention-to-treat analyses.

Abbreviations: AU: Australia; BA: behavioral activation therapy; BR: Brasil; CA: Canada; CBT: cognitive behavior therapy; Clin: recruitment from clinical samples; Comm: community recruitment; Dynamic: dynamic therapy; EU: Europe; Grp: group; Ind: individual; IPT: interpersonal psychotherapy; IR: Iran; ISR: Israel; MDD: major depressive disorder; Mood: mood disorder; N_{ses}: number of therapy sessions; PA: Pakistan; Person dis: personality disorder; PH: Combined versus pharmacotherapy; PL: Combined versus placebo; PP: Combined versus psychotherapy plus placebo; PPD: postpartum depression; PS: Combined versus psychotherapy; PST: problem-solving therapy; Psy type: type of psychotherapy; Rima: Reversible Monoamino-oxidase inhibitors; SNRI: Serotonin-noradrenalin Reuptake Inhibitors; SSRI: Selective Serotonin Reuptake Inhibitors; SST: social skills training; SUP: supportive therapy; TCA: Tricyclic antidepressants; TW: Taiwan; UK: United Kingdom; US: United States.

Selected characteristics of the included studies are presented in Table 1. Most studies (34) were aimed at adults in general, the other studies (19) were aimed at more specific target groups (patients with comorbid alcohol problems, with medical problems, comorbid personality disorders, OCD, or postpartum depression). Most studies (29) recruited only from clinical samples, while the other studies also recruited through the community (17), or used other recruitment strategies, such as systematic screening (7).

Most studies examined cognitive behavior therapy (CBT) (19), or interpersonal psychotherapy (IPT) (9), in an individual treatment format (43). SSRIs (19 studies) and TCAs (19) were used in most studies as medications; the other studies either used another type of medication (such as SNRI) (4), or used a medication protocol (11). Most studies were conducted in the US (25), or Europe (14).

The quality of the included studies varied (Table 1). Twenty-two of the 53 studies reported an adequate sequence generation. Seventeen studies reported allocation to conditions by an independent (third) party. Forty-one studies reported blinding of outcome assessors and in 32 studies intention-to-treat analyses were conducted. Thirteen studies met all four quality criteria, 18 met 2 or 3 criteria; and the remaining 22 studies had a lower quality (0 or 1 of the four criteria).

Overall effects of combined treatment compared with placebo, psychotherapy and pharmacotherapy

The effects of combined treatment compared with placebo only was g = 0.46 (95% CI: 0.21~0.70), which corresponds with a NNT of 3.91 (Table 2). Heterogeneity was low (I^2=17), although the confidence intervals around this

were broad (95% CI: 0~62). Because of the small number of studies we did not conduct any additional analyses.

Table 2. Effects of combined treatment of adult depression compared with pharmacotherapy, psychotherapy, psychotherapy + placebo, and with placebo only: Hedges' g [a)].

	N_{comp}	*g*	*95% CI*	I^2	*95% CI*	*NNT*
Combined treatment vs. placebo						
All studies	6	0.46	0.21~0.70	17	0~62	3.91
Combined treatment vs. pharmacotherapy						
All studies	41	0.38	0.26~0.49	51	29~66	4.72
4 outliers removed [b)]	37	0.34	0.25~0.44	18	0~46	5.26
HAMD only	22	0.28	0.11~0.44	56	30~73	6.41
BDI only	13	0.41	0.28~0.54	0	0~57	4.39
Combined treatment vs. psychotherapy						
All studies	19	0.34	0.20~0.48	31	0~60	5.26
One outlier removed [c)]	18	0.33	0.23~0.43	0	0~50	5.43
HAMD only	13	0.24	0.10~0.39	26	0~61	7.46
BDI only	11	0.39	0.13~0.65	54	10~77	4.59
Combined treatment vs. psychotherapy + placebo						
All studies	17	0.23	0.06~0.40	27	0~59	7.69
One outlier removed [d)]	16	0.27	0.13~0.41	0	0~52	6.58
HAMD only	9	0.33	-0.03~0.69	74	50~87	5.43
BDI only	5	0.13	-0.14~0.40	0	0~79	13.51

*: p<0.05 **: p<0.01 ***: p<0.001

Abbreviations: CI: Confidence interval; N_{comp}: number of comparisons; NNT: Numbers-needed-to-treat.

[a)] according to the random effects model; [b)] Naeem et al., 2011; Mitchell et al., 2009, Maldonado-Lopez et al., 1984; Browne et al., 2002; [c)] Shamshei et al., 2008; [d)] Bellack, 1981

The effect size indicating the difference between combined treatment and pharmacotherapy only was g = 0.38 (95% CI: 0.26~0.49; NNT=4.72). Heterogeneity was moderate (I^2=51), but dropped to low (I^2=18) after removal of 4 possible outliers. Outliers were defined as studies of which the 95% CI around the effect size did not overlap with the effect size of the pooled studies together.

The difference between combined treatment and psychotherapy only was comparable to those of combined versus pharmacotherapy (g = 0.34; 95% CI: 0.20~0.48; NNT=5.26). The already low level of heterogeneity in the main analyses dropped to zero after removal of one outlier.

The effects of combined treatment versus psychotherapy plus placebo, indicating the contribution of active medication to the effects of combined treatment, was somewhat smaller (g = 0.23; 95% CI: 0.06~0.40; NNT=7.69), with low to zero heterogeneity (I^2=27).

Study	*g*	*95% CI*	*p*	*g (95% CI)*
Appleby, 1997	0,93	0,32~1,54	0,00	
Friedman, 1975	0,38	-0,09~0,86	0,12	
Lesperance, 2007	0,22	-0,12~0,56	0,20	
Ravindran, 1999	0,86	0,19~1,52	0,01	
Reynolds, 1999	0,52	-0,20~1,25	0,16	
Wilson, 1982	0,21	-0,56~0,99	0,59	
	0,46	0,21~0,70	0,00	

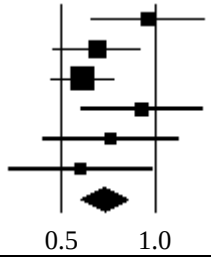

Figure 2. Standardized effect sizes of combined pharmacotherapy and psychotherapy for adult depression compared with pill placebo: Hedges' g.

Publication bias

We examined publication bias in these four main comparisons. We found some indications for possible publication bias according to Duvall and Tweedie's trim and fill procedure in the combined versus placebo conditions (number of imputed studies = 2; adjusted effect size g = 0.31; 95% CI: 0.01~0.60), but not according to Egger's test (p = 0.11). The same was true for the combined versus pharmacotherapy conditions (number of imputed studies = 2; adjusted effect size g = 0.28; 95% CI: 0.14~0.41; Egger's test p = 0.16). In the combined versus psychotherapy conditions and in the combined versus psychotherapy plus placebo neither Duvall and Tweedie's procedure nor Egger's test resulted in indications for publication bias (number of imputed studies = 0; Egger's test $p > 0.1$).

Subgroup and metaregression analyses

We conducted a series of subgroup analyses to examine the association of the effect sizes with possible moderators. Because of the small number of studies in the combined versus placebo comparisons, we did not conduct subgroup analyses for this comparison. For the other three comparisons (combined versus pharmacotherapy, versus psychotherapy, versus psychotherapy plus placebo) we examined whether the following moderators: target group (adults in general versus more specific target group), baseline severity (lower than 17 on the HAM-D; 17 to 23; 24 or higher), psychotherapy type (CBT; IPT; other), treatment format (individual versus group), type of medication (SSRI; TCA; other), and quality (met 3 or 4 criteria on the Cochrane risk of bias assessment tool versus 0 to 2 criteria). As can be seen in Table 3, we found only one significant subgroup: in the combined versus pharmacotherapy condition, the effect size was significantly smaller when SSRIs were given as medications, compared with TCAs and other medications. In the same comparison, there was a trend ($p < 0.1$) suggesting that the effect size may be smaller when IPT was used as psychological treatment, compared with CBT and other psychotherapies.

Table 3. Effects of .combined treatment of adult depression compared with pharmacotherapy, psychotherapy, psychotherapy + placebo: Subgroup analyses [a) b)] .

		N_{comp}	*g*	*95% CI*	I^2	*95% CI*	*p*	*NNT*
Combined treatment vs. pharmacotherapy								
Target group	Adults in general	29	0.39	0.24~0.53	48	20~66	0.82	
	More specific	12	0.36	0.14~0.58	59	23~78		
Baseline severity [c) d)]	17-23	18	0.42	0.26~0.58	24	0~57	0.74	
	≥ 24	6	0.49	0.13~0.85	51	0~81		
Psychotherapy type	CBT	16	0.47	0.29~0.65	46	2~70	0.08	
	IPT	9	0.14	-0.08~0.37	35	0~70		
	Other	16	0.41	0.24~0.59	36	0~65		
Format	Individual	35	0.40	0.28~0.53	54	33~69	0.20	
	Group	6	0.15	-0.21~0.52	0	0~75		
Pharmacotherapy	SSRI	14	0.18	0.01~0.35	61	30~78	0.01	
	TCA	12	0.38	0.17~0.60	0	0~58		
	Other	15	0.55	0.38~0.72	27	0~61		
Quality score	3-4	18	0.30	0.14~0.46	69	50~81	0.19	
	0-2	23	0.46	0.29~0.63	3	0~47		
Combined treatment vs psychotherapy [e)]								
Target group	Adults in general	16	0.36	0.21~0.51	31	0~62	0.48	
	More specific	3	0.22	-0.13~0.58	38	0~81		
Psychotherapy type	CBT	9	0.35	0.12~0.58	49	0~76	0.43	
	IPT	5	0.21	-0.05~0.47	0	0~79		
	Other	5	0.43	0.21~0.65	0	0~79		
Format	Individual	15	0.36	0.22~0.51	42	0~68	0.36	
	Group	4	0.15	-0.27~0.58	0	0~85		
Pharmacotherapy	SSRI	5	0.38	0.13~0.63	74	36~90	0.67	
	TCA	11	0.26	0.02~0.49	0	0~60		
	Other	3	0.40	0.14~0.66	35	0~79		
Quality score	3-4	7	0.32	0.11~0.52	41	0~75	0.78	
	0-2	12	0.36	0.16~0.56	31	0~65		
Combined treatment vs psychotherapy plus placebo								
Target group	Adults in general	7	0.10	-0.17~0.37	59	5~82	0.22	
	More specific	10	0.31	0.10~0.52	0	0~62		
Baseline severity [c)]	<17	2	0.17	-0.56~0.90	0	[f)]	0.62	
	17-23	2	-0.12	-0.92~0.68	85	[f)]		
	≥ 24	6	0.33	-0.11~0.76	56	0~82		
Psychotherapy type	CBT	4	0.24	-0.13~0.60	51	0~84	0.86	
	IPT	3	0.31	-0.07~0.70	43	0~83		
	Other	10	0.19	-0.07~0.44	25	0~64		
Format	Individual	13	0.18	-0.00~0.36	27	0~62	0.19	
	Group	4	0.46	0.08~0.84	15	0~87		
Pharmacotherapy [g)]	SSRI	8	0.32	0.06~0.57	0	0~68	0.48	
	TCA	7	0.18	-0.12~0.47	60	7~82		
Quality score	3-4	6	0.25	-0.05~0.54	24	0~67	0.86	
	0-2	11	0.22	-0.01~0.44	35	0~68		

Abbreviations: CI: Confidence interval; N_{comp}: number of comparisons; NNT: Numbers-needed-to-treat.

Table 3 (continued). Effects of .combined treatment of adult depression compared with pharmacotherapy, psychotherapy, psychotherapy + placebo: Subgroup analyses [a) b)] .

[a)] According to the random effects model.
[b)] Because the comparison combined treatment versus placebo contained only 6 comparisons, no subgroup analyses were conducted.
[c)] Only studies in which baseline severity according to the HAM-D-17 was reported, were included in these analyses.
[d)] In one study the baseline score on the HAM-D was lower than 17 (Appleby et al., 1997); this study was not included in these analyses.
[e)] The subgroup analyses on baseline severity were not conducted for this comparison, because in all studies, except one, baseline severity was moderate (17-23).
[f)] When the number of studies is smaller than 3, the 95% CI can not be calculated.
[g)] because only two studies were found in the category "other" these were not included in the analyses (Blom et al., 2007; Hernandez et al., 2004).

Table 4. Standardized regression coefficients of characteristics of studies comparing combined treatment with pharmacotherapy, psychotherapy, and psychotherapy plus placebo: Multivariate metaregression analyses

		Full model			*Parsimonious model*		
		Coef.	95% CI	*p*	Coef	95% CI	*p*
Comparison	vs pharmacotherapy	Ref					
	vs placebo	0.19	-0.13~0.52				
	vs psychotherapy	0.02	-0.18~0.21				
	vs psychother + plac	-0.10	-0.33~0.12				
Target group	Adults vs specific	-0.08	-0.26~0.10				
Baseline severity HAM-D (continuous) [a)]		0.03	-0.02~0.08				
Psychotherapy	CBT	Ref.					
	IPT	-0.27	-0.49~-0.06	*	-0.19	-0.37~-0.02	*
	Other therapy	-0.13	-0.33~0.07				
Treatment format	Individual versus group	0.03	-0.23~0.30				
Number of sessions (continuous)		-0.00	-0.02~0.02				
Medication	SSRI	Ref.					
	TCA	-0.03	-0.32~0.26				
	Other	0.20	-0.05~0.45				
Quality (continuous)		-0.00	-0.08~0.07				
Constant		0.50	0.08~0.92	*	0.39	0.30~0.48	**

*: p<0.05; **: p<0.001

[a)] Because not all studies reported baseline severity according to the HAM-D, we conducted a separate metaregression analysis for the studies in which baseline HAM-D was reported. The coefficient reported here is the result of this separate analysis.

Because all comparisons included a combined treatment (compared with another treatment), we conducted a multivariate metaregression analyses in which we included all comparisons, as well as the basic characteristics of the studies that were examined in the moderator analysis. In order to avoid collinearity, we first calculated the correlation between the characteristics of the studies that were meant to be entered into the regression model. Because we found no correlation higher than $r = 0.50$, we decided to include all variables in the model. Then we conducted a multivariate metaregression analysis, with the effect size as the dependent variable, and the comparisons as well as the other characteristics of the studies, participants, and interventions as predictors (Table 4). As can be seen in Table 4, none of the predictors was significantly associated with the effect size, except for the variable indicating that IPT was used as psychotherapy (compared with other therapies). IPT seemed to be associated with a smaller difference between combined treatment and the comparison groups.

We then conducted a (manual) back-step metaregression analysis. In this analysis, we dropped the least significant variable in each step, until only significant predictors were retained in the model (Table 4). The results of this parsimonious model also only indicated that IPT as psychotherapy was significantly associated with the effect size ($p < 0.05$).

Because baseline severity according to the HAM-D was not included in all studies, we conducted a separate meta-analysis with the studies in which baseline severity was reported (N=32). As can be seen in Table 4, we did not find that baseline severity was associated with the effect size.

Discussion

This was the first comprehensive meta-analysis of combined pharmacotherapy and psychotherapy for adult depression covering several comparisons and placebo alone. Although we found only a small number of studies comparing combined treatment against pill placebo, the results of these studies showed that combined treatment had a moderate effect size on depressive symptomatology. The resulting effect size ($g = 0.46$) was considerably larger than the effect sizes found for pharmacotherapy for depression compared with placebo ($g = 0.31$; Turner, Matthews, Linardatos, Tell, & Rosenthal, 2008) and larger than the effect sizes found for psychotherapy versus pill placebo ($g = 0.25$; Cuijpers et al., 2014). This suggests that combined treatment is superior to single treatments when compared against pill placebo within the same trials. However, this should be interpreted with caution, because the confidence interval around the effect size for combined treatment versus placebo were broad as a result of the small number of studies. Furthermore, there were some indications for publication bias and after adjustment for this bias, the effect size was considerably smaller.

We could also confirm in this meta-analysis that combined treatment is significantly more effective than pharmacotherapy alone, than psychotherapy

alone, and even against psychotherapy plus placebo. For each of these comparisons several dozens of comparisons were available. These results were in line with earlier meta-analyses examining each of these comparisons (De Maat et al., 2007; Cuijpers et al., 2014; Pampanolla et al., 2004).

In the multivariate metaregression, in which we included all comparisons simultaneously, we did not find that the effect size for combined treatment versus placebo was significantly higher than combined versus pharmacotherapy, or combined versus psychotherapy (with or without placebo). So, although the effects for combined versus placebo were larger than for the other comparisons, this was not significant. However, this can very well be caused by the broad confidence intervals around the effect size for combined treatment versus placebo.

An unexpected finding was that IPT seemed to result in lower effect sizes than CBT and other psychotherapies. This is unexpected as earlier meta-analyses found that IPT may be somewhat more effective than other psychotherapies (Cuijpers, van Straten, Andersson, & van Oppen, 2008; Barth, Munder, Gerger, Nuesch, Trelle, Znoj, et al., 2013). However, this finding should be considered with caution because it is not the result of direct comparisons with other therapies, which would provide much stronger evidence. Furthermore, it may very well be that this finding is caused by a third variable associated with both the effect size and this particular characteristic, but that was not examined in the metaregression analysis.

From a clinical point of view the results of this meta-analysis raise many questions. First, in regular care it is often the case that medication and psychotherapy is provided by different clinicians and sometimes even at different clinics, with antidepressant medication often being prescribed in primary care and psychotherapy delivered in secondary care or settings outside of the hospital. Moreover, funding of services differs across countries as well with different structures for medication and psychotherapy. Second, we cannot exclude the possibility that different medications and different psychotherapies work more or less well together. In this meta-analysis many studies used CBT, but even within CBT there are differences with more or less emphasis on behavioral and cognitive aspects. Third, we did not cover the costs of treatment in this meta-analysis as it is obvious that two simultanous treatments cost more than one. The NNTs give some indications here but perhaps the most important clinical implication for caregivers is that it may be worthwhile to add medication to psychotherapy and vice versa. From a stepped care perspective, augmenting treatment components might be especially helpful when initial monotherapy does not lead to a rapid response. Sequenced treatment approaches, in which additional treatment is only provided when it is needed or when it is known to improve long-term outcomes, might prove to offer a better risk/benefit ratio in the long-term (Forand, DeRubeis & Amsterdam 2013).

In addition to the added value of psychotherapy to medication, there is preliminary evidence that psychotherapy has longer term effects than medication

even when staying on the medication (Cuijpers, Hollon, Van Straten, Bockting, Berking, & Andersson, 2013). If this is the case when psychotherapy is provided together with medication as well is not yet known and will require more studies and longer term outcomes. A final clinical implication has to do with severity as there are still many unknowns regarding response rates for different subgroups. As mentioned earlier in this paper a previous meta-analysis showed smaller effects of psychotherapy for dysthymia and chronic depression (Cuijpers, et al., 2010), and it is likely that the moderating effect of chronicity cannot be detected by means of cut-off scores only done in this meta-analysis.

The results of this meta-analysis should be considered with caution because of its limitations. First, the number of studies comparing combined treatment with placebo was small. Second, the quality of many of the included studies was not optimal, although we did not find indications that the quality was associated with the effect sizes. However, not finding such associations does not automatically imply that it does not exist, especially when the number of studies is small, which was the case here.

Despite these limitations, we can conclude that combined treatment of depression may be the best treatment available for adult depression, and that it is significantly more effective than placebo, pharmacotherapy, psychotherapy and the combination of psychotherapy and placebo.

REFERENCES

References marked with an asterisk are included in the meta-analysis

Andersson, G., & Cuijpers, P. (2009). Internet-based and other computerized psychological treatments for adult depression: A meta-analysis. Cognitive Behaviour Therapy, 38, 196-205.

* Appleby, L., Warner, R., Whitton, A., & Faragher, B. (1997) A controlled study of fluoxetine and cognitive-behavioural counselling in the treatment of postnatal depression. British Medical Journal, 314, 932-936.

Barth, J., Munder, T., Gerger, H., Nuesch, E., Trelle, S., Znoj, H., Juni, P., & Cuijpers, P. (2013). Comparative efficacy of seven psychotherapeutic interventions for depressed patients: A network meta-analysis. Plos Medicine, 10(5): e1001454.

Bauer, M., Pfennig, A., Severus, E., Whybrow, P.C., Angst, J., Möller, H.J., & Task Force on Unipolar Depressive Disorders (2013). World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: update 2013 on the acute and continuation treatment of unipolar depressive disorders. World Journal of Biological Psychiatry, 14, 334-385.

* Beck, A.T., Hollon, S.D., Young, J.E., Bedrosian, R.C., & Budenz, D. (1985). Treatment of depression with cognitive therapy and amitriptyline. Archives of General Psychiatry, 42, 142-148.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. Archives of General Psychiatry 4, 561-571.

* Bellack, A.S., Hersen, M., & Himmelhoch, J. (1981) Social skills training compared with pharmacotherapy and psychotherapy in the treatment of unipolar depression. American Journal of Psychiatry, 138, 1562-1567.

* Bellino, S., Zizza, M., Camilla, R., & Filippo, B. (2006) Combined treatment of major depression in patients with borderline personality disorder: A comparison with pharmacotherapy. Canadian Journal of Psychiatry, 51, 453-460.

* Blackburn, I.M., Bishop, S., Glen, A.I., Whalley, L.J., & Christie, J.E. (1981) The efficacy of cognitive therapy in depression: a treatment trial using cognitive therapy and pharmacotherapy, each alone and in combination. British Journal of Psychiatry, 139, 181-189.

* Bloch, M., Meiboom, H., Lorberblatt, M., Bluvstein, I., Aharonov, I.,& Schreiber, S. (2012). The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study. Journal of Clinical Psychiatry, 73, 235-241.

* Blom, M.B., Spinhoven, P., Hoffman, T., Jonker, K., Hoencamp, E., Haffmans, P.M., & van Dyck, R. (2007). Severity and duration of depression, not personality factors, predict short term outcome in the treatment of major depression. Journal of Affective Disorders, 104, 119-126.

Borenstein, M., Hedges, L.V., Higgins, J.P.T., & Rothstein, H.R. (2009). Introduction to meta-analysis. Chichester, UK: Wiley.

* Browne, G., Steiner, M., Roberts, J., Gafni, A., Byrne, C., Dunn, E., Bell, B., Mills, M., Chalklin, L., Wallik, D., & Kraemer, J. (2002) Sertraline and/or interpersonal psychotherapy for patients with dysthymic disorder in primary care: 6-month comparison with longitudinal 2-year follow-up of effectiveness and costs.. Journal of Affective Disorders, 68, 317-330.

* Burnand, Y., Andreoli, A., Kolatte, E., Venturini, A., & Rosset, N. (2002) Psychodynamic paychotherapy and clomipramine in the treatment of major depression. Psychiatric Services, 53, 585-589.

Cuijpers, P., van Straten, A., Warmerdam, L., & Andersson, G. (2008). Psychological treatment of depression: A meta-analytic database of randomized studies. BMC Psychiatry, 8, 36.

Cuijpers, P., van Straten, A., Andersson, G., & van Oppen, P. (2008). Psychotherapy for depression in adults: A meta-analysis of comparative outcome studies. Journal of Consulting and Clinical Psychology, 76, 909-922.

Cuijpers, P., Geraedts, A.S., van Oppen, P., Andersson, G., Markowitz, J.C., van Straten, A. (2011). Interpersonal psychotherapy of depression: A meta-analysis. American Journal of Psychiatry, 168, 581-592.

Cuijpers, P., Berking, M., Andersson, G., Quigley, L., Kleiboer, A., & Dobson, K.S. (2013). A meta-analysis of cognitive behavior therapy for adult depression, alone and in comparison to other treatments. Canadian Journal of Psychiatry, 58, 376-385.

Cuijpers, P., Driessen, E., Hollon, S.D., van Oppen, P., Barth, J., & Andersson, G. (2012). The efficacy of non-directive supportive therapy for adult depression: A meta-analysis. Clinical Psychology Review, 32, 280-291.

Cuijpers, P., Sijbrandij, M., Koole, S.L., Andersson, G., Beekman, A.T., & Reynolds III, C.F. (2013). The efficacy of psychotherapy and pharmacotherapy in treating

depressive and anxiety disorders: a meta-analysis of direct comparisons. World Psychiatry, 12, 137–148.

Cuijpers, P., Turner, E.H., Mohr, D.C., Hofmann, S.G., Andersson, G., Berking, M., & Coyne, J. (2014). Comparison of psychotherapies for adult depression to pill placebo control groups: A meta-analysis. Psychological Medicine, 44, 685-695.

Cuijpers, P., Hollon, S., Van Straten, A., Bockting, C., Berking, M., & Andersson, G. (2013). Does cognitive behaviour therapy have an enduring effect that is superior to keeping patients on continuation pharmacotherapy? A meta-analysis. BMJ Open, 3, e002542.

Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S. D., & Andersson, G. (2010). Psychotherapy for chronic major depression and dysthymia: A meta-analysis. Clinical Psychology Review, 30, 51-62.

Cuijpers, P., van Straten, A., & Warmerdam, L. (2008). Are individual and group treatments equally effective in the treatment of depression in adults? A meta-analysis. European Journal of Psychiatry, 22, 38-51.

Cuijpers, P., van Straten, A., Schuurmans, J., van Oppen, P., Hollon, S. D., & Andersson, G. (2010). Psychotherapy for chronic major depression and dysthymia: A meta-analysis. Clinical Psychology Review, 30, 51-62.

Cuijpers, P., Donker, T., van Straten, A., & Andersson, G. (2010). Is guided self-help as effective as face-to-face psychotherapy for depression and anxiety disorders? A meta-analysis of comparative outcome studies. Psychological Medicine, 40, 1943-1957.

* de Jonghe, F., Hendricksen, M., van Aalst, G., Kool, S., Peen, V., Van, R., van den Eijnden, E., & Dekker, J. (2004) Psychotherapy alone and combined with pharmacotherapy in the treatment of depression. British Journal of Psychiatry, 185, 37-45.

* de Jonghe, F., Kool, S., van Aalst, G., Dekker, J., & Peen, J. (2001) Combining psychotherapy and antidepressants in the treatment of depression. Journal of Affective Disorders, 64, 217-229.

de Maat, S.M., Dekker, J., Schoevers, R.A., & de Jonghe, F. (2007). Relative efficacy of psychotherapy and combined therapy in the treatment of depression: a meta-analysis. European Psychiatry, 22, 1-8.

* de Mello, M.F., Myczcowisk, L.M., & Menezes, P.R. (2001) A randomized controlled trial comparing moclobemide and moclobemide plus interpersonal psychotherapy in the treatment of dysthymic disorder. Journal of Psychotherapy Practice and Research, 10, 117-123.

* Denton, W. H., Wittenborn, A.K., & Golden, R.N. (2012). Augmenting antidepressant medication treatment of depressed women with emotionally focused therapy for couples: a randomized pilot study. Journal of Marital and Family Therapy, 38, Suppl 1, 23-38.

* Dozois, D.J.A., Bieling, P.J., Patelis-Siotis, I., Hoar, L., Chudzik, S., McCabe, K., & Westra, H.A. (2009) Changes in Self-Schema Structure in Cognitive Therapy for Major Depressive Disorder: A Randomized Clinical Trial. Journal of Consulting and Clinical Psychology 77, 1078-1088.

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics, 56, 455-463.

Ekers, D., Richards, D., & Gilbody S. (2008). A meta-analysis of randomized trials of behavioural treatment of depression. Psychological Medicine, 38, 611–623.

* Finkenzeller, W., Zobel, I., Rietz, S., Schramm, E., & Berger, M. (2009) [Interpersonal psychotherapy and pharmacotherapy for post-stroke depression. Feasibility and effectiveness]. Nervenarzt, 80, 805-812.

Forand, N.R., DeRubeis, R.J., & Amsterdam, J.D. (2013). The Combination of Psychotherapy and Medication in the Treatment of Mental Disorders." In Bergin and Garfield's Handbook of Psychotherapy and Behavior Change, 6th Edition. Edited by Lambert, MJ. -. Hoboken, NJ, US|USA: Wiley.

* Friedman, A. (1975) Interaction of drug therapy with marital therapy in depressed patients. Archives of General Psychiatry, 32, 619-637.

Gartlehner, G., Hansen, R.A., Morgan, L.C., Thaler, K., Lux, L., Van Noord, M., Mager, U., Thieda, P., Gaynes, B.N., Wilkins, T., Strobelberger, M., Lloyd, S., Reichenpfader, U., Lohr, K.N. (2012). Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder; An Updated Meta-analysis. Annals of Internal Medicine, 155, 772-785.

Gloaguen, V., Cottraux, J., Cucherat, M., & Blackburn, I.M. (1998). A meta-analysis of the effects of cognitive therapy in depressed patients. Journal of Affective Disorders, 49, 59–72.

Hamilton, M. (1960). A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry, 23, 56–62.

* Hautzinger, M., de Jong-Meyer, R., Treiber, R., Rudolf, G. A. E., & Thien, U. (1996). Wirksamkeit Kognitiver Verhaltenstherapie, Pharmacotherapie und deren Kombination bei nicht-endogenen, unipolaren Depression. Zeitschrift für Klinische Psychologie, 25, 130-145.

Hedges, L.V., & Olkin, I. (1985). Statistical methods for meta-analysis. San Diego, CA: Academic Press.

* Hellerstein, D.J., Little, S.A.S., Samstag, L.W., Batchelder, S., Muran, C.J., Fedak, M., Kreditor, D., Rosenthal, R.N., & Winston, R. (2001) Adding group psychotherapy to medication treatment in dysthymia: A randomized prospective pilot study. Journal of Psychotherapy Practice and Research, 10, 93-103.

* Hernandez-Avila, C.A., Modesto-Lowe, V., Feinn, R., & Kranzler, H.R. (2004). Nefazodone treatment of comorbid alcohol dependence and major depression. Alcohol Clinical and Experimental Research, 28, 433-440.

Higgins, J.P.T., & Green, S. (2011). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org.

* Hollon, S.D., DeRubeis, R.J., Evans, M.D., Wiemer, M.J., Garvey, M.J., Grove, W.M., & Tuason, V.B. (1992) Cognitive therapy and pharmacotherapy for depression: singly and in combination. Archives of General Psychiatry, 49, 774-781.

* Hsiao, F.H., Jow, G.M., Lai, Y.M., Chen, Y.T., Wang, K.C., Ng, S.M., Ho, R.T.H., Chan, C.L.W., & Yang, T.T. (2011) The long-term effects of psychotherapy added to pharmacotherapy on morning to evening diurnal cortisol patterns in outpatients with major depression. Psychotherapy and Psychosomatics, 80, 166-172.

Ioannidis, J.P.A., Patsopoulos, N.A., Evangelou, E. (2007). Uncertainty in heterogeneity estimates in meta-analyses. British Medical Journal, 335, 914–916.

* Keller, M.B., McCullough, J.P., Klein, D.N., Arnow, B., Dunner, D.L., Gelenberg, A.J., Markowitz, J.C., Nemeroff, C.B., Russell, J.M., Thase, M.E., Trivedi, M.H., & Zajecka, J.A. (2000) comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. New England Journal of Medicine, 342, 1462-1470.

Kraemer, H.C., & Kupfer, D.J. (2006). Size of treatment effects and their importance to clinical research and practice. Biological Psychiatry, 59, 990-996.

* Lam, R.W., Parikh, S.V., Ramasubbu, R., Michalak, E.E., Tam, E.M., Axler, A., Yatham, L.N., Kennedy, S.H., & Manjunath, C.V. (2013). Effects of combined pharmacotherapy and psychotherapy for improving work functioning in major depressive disorder. British Journal of Psychiatry, 203, 358-365.

Laupacis, A., Sackett, D.L., & Roberts, R.S. (1988). An assessment of clinically useful measures of the consequences of treatment. New England Journal of Medicine, 318, 1728–1733.

* Lespérance, F., Frasure-Smith, N., Koszycki, D., Lalibert, M.A., van Zyl, L.T., Baker, B., Swenson, J.R., Ghatavi, K., Abramson, B.L., Dorian, P., Guertin, M.C., & CREATE Investigators (2007) Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial. Journal of the American Medical Association, 297, 367-379.

* Lynch, T.R., Cheavens, J.S., Cukrowicz, K.C., Thorp, S.R., Bronner, L., Beyer, J. (2007) Treatment of older adults with co-morbid personality disorder and depression: A dialectical behavior therapy approach. International Journal of Geriatric Psychiatry, 22, 131-143.

* Macaskill, N.D., & Macaskill, A. (1996) Rational-emotive therapy plus pharmacotherapy vs. Pharmacotherapy alone in the treatment of high cognitive dysfunction depression. Cognitive Therapy and Research, 20, 575-592.

* Maina, G., Rosso, G., Rigardetto, S., Piat, S.C., & Bogetto, F. (2010). No effect of adding brief dynamic therapy to pharmacotherapy in the treatment of obsessive-compulsive disorder with concurrent major depression. Psychotherapy and Psychosomatics, 79, 295-302.

* Maldonado Lopez, A. (1984). Behavioural therapy and depression: an experimental analysis of the interaction between cognitive and behavioural therapies and pharmacological therapy in depressed people. Revista de Psicologia General y Aplicada, 39, 517-535.

Malouff, J.M., Thorsteinsson, E. B., & Schutte, N.S. (2007). The efficacy of problem solving therapy in reducing mental and physical health problems: a meta-analysis. Clinical Psychology Review, 27, 46–57.

* Markowitz, J.C., Kocsis, J.H., Bleiberg, K.L., Christos, P.J., & Sacks, M. (2005) A comparative trial of psychotherapy and pharmacotherapy for "pure" dysthymic patients. Journal of Affective Disorders, 89, 167-175.

* Markowitz, J.C., Kocsis, J.H., Fishman, B., Spielman, L.A., Jacobsberg, L.B., Frances, A.J., Klerman, G.L., & Perry, S.W. (1998) Treatment of depressive symptoms in human immunodeficiency virus-positive patients. Archives of General Psychiatry, 55, 452-457.

* McGrath, P.J., Nunes, E.V., Stewart, J.W., Goldman, D., Agosti, V., Ocepek-Welikson, K., & Quitkin, F.M. (1996). Imipramine treatment of alcoholics with primary

depression: A placebo-controlled clinical trial. Archives of General Psychiatry, 53, 232-240.

* Misri, S., Reebye, P., Corral, M., & Milis, L. (2004) The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. Journal of Clinical Psychiatry, 65, 1236-1241.

* Mitchell, P.H., Veith, R.C., Becker, K.J., Buzaitis, A., Cain, K.C., Fruin, M., et al. (2009). Brief psychosocial-behavioral intervention with antidepressant reduces poststroke depression significantly more than usual care with antidepressant antidepressant: Living Well With Stroke: randomized, controlled trial. Stroke, 40, 3073-3078.

* Moak, D.H., Anton, R.F., Latham, P.K., Voronin, K.E., Waid, R.L., & Durazo-Arvizu, R. (2003) Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. Journal of Clinical Psychopharmacology, 23, 553-562.

* Murphy, G.E., Simons, A.D., Wetzel, R.D., & Lustman, P.J. (1984) Cognitive therapy and pharmacotherapy; Singly and together in the treatment of depression. Archives of General Psychiatry, 41, 33-41.

* Mynors-Wallis, L.M., Gath, D.H., Day, A., & Baker, F. (2000) Randomised controlled trial of problem solving treatment, antidepressant medication, and combined treatment for major depression in primary care. British Medical Journal, 320, 26-30.

* Naeem, F., Waheed, W., Gobbi, M., Ayub, M., & Kingdon, D. (2011) Preliminary evaluation of culturally sensitive CBT for depression in Pakistan: Findings from Developing Culturally-sensitive CBT Project (DCCP). Behavioural and Cognitive Psychotherapy, 39, 165-73.

Orsini, N., Higgins, J., Bottai, M., & Buchan, I. (2005). Heterogi: Stata module to quantify heterogeneity in a meta-analysis (http://EconPapers.repec.org/RePEc:boc:bocode:s449201). Accessed 3 February 2014.

Pampallona, S., Bollini, P., Tibaldi, G., Kupelnick, B., & Munizza, C. (2004). Combined pharmacotherapy and psychological treatment for depression: A systematic review. Archives of General Psychiatry, 61, 714-719

Posternak, M. A., & Zimmerman, M. (2007). Therapeutic effect of follow-up assessments on antidepressant and placebo response rates in antidepressant efficacy trials: meta-analysis. British Journal of Psychiatry, 190, 287-292.

* Ravindran, A.V., Anisman, H., Merali, Z., Charbonneau, Y., Telner, J., Bialik, R.J., Wiens, A., Ellis, J., & Griffiths, J. (1999) Treatment of primary dysthymia with group cognitive therapy and pharmacotherapy: clinical symptoms and functional impairments. American Journal of Psychiatry, 156, 1608-1617.

* Reynolds, C.F., Miller, M.D., Pasternak, R.E., Frank, E., Perel, J.M., Cornes, C., Houck, P.R., Mazumdar, S., Dew, M.A., & Kupfer, D.J. (1999) Treatment of bereavement-related major depressive episodes in later life: a controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. American Journal of Psychiatry, 156, 202-208.

* Roth, D., Bielski, R., Jones, M., Parker, W., & Osborn, G. (1982) A comparison of self-control therapy and combined self-control therapy and anti-depressant medication in the treatment of depression. Behavior therapy, 13, 133-144.

* Rush, A.J., & Watkins, J.T. (1981) Group versus individual cognitive therapy: A pilot study. Cognitive therapy and Research, 5, 95-103.

* Schiffer, R.B., & Wineman, N.M. (1990). Antidepressant pharmacotherapy of depression associated with multiple sclerosis. American Journal of Psychiatry, 147, 1493-1497.

* Shamsaei, F., Rahimi, A., Zarabian, M.K., & Sedehi, M. (2008) Efficacy of pharmacotherapy and cognitive therapy, alone and in combination in major depressive disorder. Hong Kong Journal of Psychiatry, 18, 76 – 80.

Shedler, J. (2010). The efficacy of psychodynamic psychotherapy. American Psychologist, 65, 98-109.

* Sirey, J.A., Bruce, M.L., & Alexopoulos, G.S. (2005). The Treatment Initiation Program: an intervention to improve depression outcomes in older adults. American Journal of Psychiatry, 162, 184–186.

* Stravynski, A., Verreault, R., Gaudette, G., Langlois, R., Gagnier, S., & Larose, M. (1994). The treatment of depression with group behavioural-cognitive therapy and imipramine. Canadian Journal of Psychiatry, 39, 387-390.

* Targ, E.F., Karasic, D.H., Diefenbach, P.N., Anderson, D.A., Bystritsky, A., & Fawzy, F.I. (1994) Structured group therapy and fluoxetine to treat depression in HIV-positive persons. Psychosomatics, 35, 132-137.

* Thompson, L.W., Coon, D.W., Gallagher-Thompson, D., Sommer, B.R., & Koin, D. (2001). Comparison of desipramine and cognitive/behavioral therapy in the treatment of elderly outpatients with mild-to-moderate depression. American Journal of Geriatric Psychiatry, 9, 225–240.

Turner, E.H., Matthews, A.M., Linardatos, E., Tell, R.A., & Rosenthal, R. (2008). Selective publication of antidepressant trials and its influence on apparent efficacy. New England Journal of Medicine, 358, 252–260.

* Weissman, M.M., Prusoff, B.A., Dimascio, A., Neu, C., Goklaney, M., & Klerman, G.L. (1979) The efficacy of drugs and psychotherapy in the treatment of acute depressive episodes. American Journal of Psychiatry, 136, 555-558.

* Wiles, N., Thomas, L., Abel, A., Ridgway, N., Turner, N., Campbell, J., Garland, A., Hollinghurst, S., Jerrom, B., Kessler, D., Kuyken, W., Morrison, J., Turner, K., Williams, C., Peters, T., & Lewis, G. (2013). Cognitive behavioural therapy as an adjunct to pharmacotherapy for primary care based patients with treatment resistant depression: results of the CoBalT randomised controlled trial. Lancet, 381, 375–384.

* Wiles, N.J., Hollinghurst, S., Mason, V., Musa, M., Burt, V., Hyde, J., Jerrom, B., Lewis, G., & Kessler, D. (2008) A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: A pilot study. Behavioural and Cognitive Psychotherapy, 36, 21-33.

* Wilson, P.H. (1982) Combined pharmacological and behavioural treatment of depression. Behaviour Research and Therapy, 20, 173-184.

* Yang, T.T., Hsiao, F.H., Wang, K.C., Ng, S.M., Ho, R.T., Chan, C.L., Lai, Y.M., & Chen, Y.T. (2009 June) The effect of psychotherapy added to pharmacotherapy on cortisol responses in outpatients with major depressive disorder. Journal of Nervous and Mental Disease, 197, 401-406.

* Zisook, S., Peterkin, J., Goggin, K.J., Sledge, P., Atkinson, J.H., & Grant, I. (1998) Treatment of major depression in HIV-seropositive men. HIV Neurobehavioral Research Center Group. Journal of Clinical Psychiatry, 59, 217-224.